CHAPTER 37

TOFACITINIB IN PSORIASIS

Burhan Engin, MD, Uğur Çelik MD, Zekayi Kutlubay, MD, Server Serdaroğlu, MD, Yalçın Tüzün, MD

INTRODUCTION

In the last years, biologic therapy options for severe psoriasis enable good responses with less side effects.[1] Conventional therapies may have insufficient efficacy, adverse events and teratogenicity.[2] For all that, there are still patients with psoriasis irresponsive to these therapies. Researches for new molecules targeting immune mechanisms involved in inflammatory processes are going on.

T lymphocytes, especially T helper-1 and T helper-17 subtypes, tumor necrosis factor (TNF)-α, interferon (IFN)-γ, interleukin (IL)-1, IL-6, IL-12, IL-15, IL-17, IL-20 and IL-23 have crucial roles in psoriasis pathogenesis.[1, 3]

Protein kinases are significant constituents of intracellular signaling pathways. These pathways are essential for growth and differentiation of cells and immune responses. JAK-STAT (Janus kinase-signal transducer and activator of transcription) system, which is important for lymphocyte functions, provides transmission of outer signals into the cell nucleus.[4, 5] Tofacitinib, formerly known as CP-690550 is a new molecule that inhibits this pathway and a promising drug for the treatment of inflammatory diseases such as psoriasis and rheumatoid arthritis.[1, 6]

All TNF inhibitors require parenteral administration but tofacitinib is a small molecule providing oral usage.[1] We need further head-to-head trials to be able to choice best option for patients.

Mechanism of Action

Transduction of chemical signals into the cell is essential for cellular functions such as inflammation and cell division. Protein kinases are cellular enzymes that are involved in signal transduction. These kinases activate or deactivate other proteins via phosphorylation. Receptors on cell membrane may have their own kinase activity but some receptors need these kinases to transmit their signals.[2, 4]

There are different groups of protein kinases, one of which is protein tyrosine kinase (PTK) group. Their names are associated with tyrosine residues they phosphorylated. Janus kinases (JAKs) are cytoplasmic protein tyrosine kinases. JAKs phosphorylate the signal transducer and activator of transcription (STAT) proteins and latter control nuclear transcription of particular genes.[4, 5]

There are four JAK types identified and cytokines associated with them shown in table 1.

Table 1. JAKs and related cytokine receptors[1]

JAK-1	IL-6, IL-10, IFN and receptors contain the common gamma chain (IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21).
JAK-2	IL-12, IL-23 and hematopoietic receptors.
JAK-3	Most specific type and associated with receptors contain the common gamma chain like JAK-1.
TYK-2	IFN, IL-12 and IL-23 receptors.

As a result, JAK-STAT system proteins contribute to activation of inflammatory cells such as lymphocytes, macrophages and neutrophils. They cooperate with receptors especially of common gamma chain family.[2] Tofacitinib is one of the JAK system inhibitors being searched for the treatment of inflammatory diseases. It inhibits JAK-3 (and JAK-1 to a lesser extent), which has a crucial role for cytokines associated with lymphocyte proliferation, differentiation and apoptosis. JAK-3 inhibition causes immunosuppression.[4, 7]

INDICATIONS

JAKs are cytoplasmic tyrosine kinases that play role in signaling pathway of particular cytokines. Inhibition of these enzymes has immunosuppressive effects. Tofacitinib, a selective JAK-3 inhibitor, is being searched for psoriasis, psoriatic arthritis, rheumatoid arthritis, inflammatory bowel diseases, ankylosing spondylitis, xerophthalmia and transplant rejection.[7]

JAK-3 inhibition is related with decreased functions of interleukins some of which are important for psoriasis pathogenesis. These cytokines are IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 while IL-15 has a special importance.[1, 3]

Oral tofacitinib is approved by FDA for the treatment of rheumatoid arthritis. Recommended dose is 5 mg twice daily.[8] In phase III trials, it was found effective in

bronchitis, cough, herpes zoster, anemia, dizziness, vomiting, gastritis, and abdominal pain, loss of appetite, back pain, peripheral edema, influenza, and congestive heart failure. Adverse events observed in trials are shown in table 3.[8]

Table 3. Adverse events during trials[8]

Occasional	Rare
Upper respiratory tract infection	Pruritus
Headache	Neutropenia
Nasopharyngitis	Myocardial infarction
Diarrhea	Congestive heart failure
Nausea	Hepatic steatosis
Urinary tract infection	Sepsis
Hypertension	Pneumonia
Bronchitis	Pyelonephritis
Anemia	Tuberculosis
Hypercholesterolemia	Encephalitis
Abdominal pain	Necrotizing fasciitis
Vomiting	Bacterial arthritis
Constipation	Viral infections
Increased alanine aminotransferase	Cellulitis
Dizziness	Increased blood creatinine
Gastroenteritis	Abnormal liver function tests
Peripheral edema	Tendonitis
Back pain	Non-melanoma skin cancers
Rheumatoid arthritis	Other cancers
Arthralgia	Paresthesia
Pyrexia	Herpes zoster

DRUG INTERACTIONS

In a study of patients with rheumatoid arthritis, methotrexate did not change the pharmacokinetics of tofacitinib. Co-administration of fluconazole increased mean tofacitinib levels due to inhibition of cytochrome P450 enzyme in a different study. Potent inhibitors of CYP3A4 (ketoconazole) and CYP2C19 (fluconazole), potent inducers of CYPs (rifampin) are possible drugs interact with. It is not recommended to combine with tacrolimus, cyclosporine and azathioprine to avoid the risk of added immunosuppression. It is not necessary dose adjustment when using with metformin, midazolam and oral contraceptives (ethinyl estradiol and levonorgestrel).[8, 39]

FOLLOW UP

Vital signs such as pulse rate and blood pressure should be checked at the beginning and during treatment. Tofacitinib usage has the risk of serious infections and malignancies. Patients must be monitored about malignancies and opportunistic infections such as tuberculosis (including patients who are negative for latent tuberculosis), pneumonia, candidiasis, invasive fungal infections, and herpes zoster and cytomegalovirus infections. For patients with increased skin cancer risk, skin examination is recommended at follow up visits. JAK system is related to hematopoiesis so hematological parameters need evaluation. Hemoglobin, neutrophils, lymphocytes, lipids, liver enzymes and serum creatinine levels should be monitored during treatment.[8]

SUMMARY

Protein kinases are important components of intracellular signaling pathways associated with growth and differentiation of immune cells. JAKs are protein kinases becoming the targets of new searches about the treatment of inflammatory diseases.[1, 2, 3] Tofacitinib is a new orally used small molecule that inhibits JAK-3. In trials, it has favorable results for the treatment of inflammatory diseases, especially rheumatoid arthritis and psoriasis.[7] FDA approved oral tofacitinib for rheumatoid arthritis as 5 mg twice daily dosage.[8] Phase II and phase III trials of oral tofacitinib for psoriasis reported positive results.[15, 16] Topical form was also found effective in patients with mild to moderate plaque psoriasis.[21] Tofacitinib is also being searched for the treatment of transplant rejection, inflammatory bowel diseases, ankylosing spondylitis and xerophthalmia.[7]

Tofacitinib is an immunosuppressive and it may have serious adverse events such as infections including tuberculosis, malignancies, cardiovascular diseases, renal failure and death. More common side effects are nausea, headache, milder infections, increased serum cholesterol, aminotransferase and creatinine levels, anemia and neutropenia. Patients must be monitored during treatment for these unwanted events. Further trials are needed to learn about long term efficacy and safety.[8]

REFERENCES

1. Ortiz-Ibanez K, Alsina MM, Munoz-Santos C. Tofacitinib and other kinase inhibitors in the treatment of psoriasis. Actas Dermosifiliogr 2013; 104: 304-310.
2. Hsu L, Armstrong AW. JAK inhibitors: treatment efficacy and safety profile in patients with psoriasis. J Immunol Res 2014: 283617.
3. Gan EY, Chong WS, Tey HL. Therapeutic strategies in psoriasis patients with psoriatic arthritis: focus on new agents. BioDrugs 2013; 27: 359-373.
4. Vijayakrishnan L, Venkataramanan R, Gulati P. Treating inflammation with the Janus kinase inhibitor CP-690,550. Trends Pharmacol Sci 2011; 32: 25-34.
5. Ghoreschi K, Gadina M. Jakpot! New small molecules in autoimmune and inflammatory diseases. Exp Dermatol 2014; 23: 7-11.
6. Vafadari R, Weimar W, Baan CC. Phosphospecific flow cytometry for pharmacodynamic drug monitoring: analysis of the JAK-STAT signaling pathway. Clin Chim Acta 2012; 413: 1398-1405.
7. Tofacitinib. Drugs R D 2010; 10: 271-284. Review. Erratum in: Drugs R D 2012; 12: 41-43.
8. Xeljanz Product Monograph by Pfizer, available at URL: http://www.pfizer.ca/en/our_products/products/monograph/342

9. Fleischmann R, Kremer J, Cush J, Schulze-Koops H, Connell CA, Bradley JD, Gruben D, Wallenstein GV, Zwillich SH, Kanik KS; ORAL Solo Investigators. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. N Engl J Med 2012; 367: 495-507.
10. Burmester GR, Blanco R, Charles-Schoeman C, Wollenhaupt J, Zerbini C, Benda B, Gruben D, Wallenstein G, Krishnaswami S, Zwillich SH, Koncz T, Soma K, Bradley J, Mebus C; ORAL Step investigators. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. Lancet 2013; 381: 451-460.
11. Kremer J, Li ZG, Hall S, Fleischmann R, Genovese M, Martin-Mola E, Isaacs JD, Gruben D, Wallenstein G, Krishnaswami S, Zwillich SH, Koncz T, Riese R, Bradley J. Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. Ann Intern Med 2013; 159: 253-261.
12. van der Heijde D, Tanaka Y, Fleischmann R, Keystone E, Kremer J, Zerbini C, Cardiel MH, Cohen S, Nash P, Song YW, Tegzová D, Wyman BT, Gruben D, Benda B, Wallenstein G, Krishnaswami S, Zwillich SH, Bradley JD, Connell CA; ORAL Scan Investigators. Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. Arthritis Rheum 2013; 65: 559-570.
13. Lee EB, Fleischmann R, Hall S, Wilkinson B, Bradley JD, Gruben D, Koncz T, Krishnaswami S, Wallenstein GV, Zang C, Zwillich SH, van Vollenhoven RF; ORAL Start Investigators. Tofacitinib versus methotrexate in rheumatoid arthritis. N Engl J Med 2014; 370: 2377-2386.
14. van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, García Meijide JA, Wagner S, Forejtova S, Zwillich SH, Gruben D, Koncz T, Wallenstein GV, Krishnaswami S, Bradley JD, Wilkinson B; ORAL Standard Investigators. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med 2012; 367: 508-519.
15. Boy MG, Wang C, Wilkinson BE, Chow VF, Clucas AT, Krueger JG, Gaweco AS, Zwillich SH, Changelian PS, Chan G. Double-blind, placebo-controlled, dose-escalation study to evaluate the pharmacologic effect of CP-690,550 in patients with psoriasis. J Invest Dermatol 2009; 129: 2299-2302.
16. Papp KA, Menter A, Strober B, Langley RG, Buonanno M, Wolk R, Gupta P, Krishnaswami S, Tan H, Harness JA. Efficacy and safety of tofacitinib, an oral Janus kinase inhibitor, in the treatment of psoriasis: a Phase 2b randomized placebo-controlled dose-ranging study. Br J Dermatol 2012; 167: 668-677.
17. Mamolo C, Harness J, Tan H, Menter A. Tofacitinib (CP-690,550), an oral Janus kinase inhibitor, improves patient-reported outcomes in a phase 2b, randomized, double-blind, placebo-controlled study in patients with moderate-to-severe psoriasis. J Eur Acad Dermatol Venereol 2013 Jan 7.
18. Strober B, Buonanno M, Clark JD, Kawabata T, Tan H, Wolk R, Valdez H, Langley RG, Harness J, Menter A, Papp K. Effect of tofacitinib, a Janus kinase inhibitor, on haematological parameters during 12 weeks of psoriasis treatment. Br J Dermatol 2013; 169: 992-999.
19. Bissonnette R, Iversen L, Sofen H, Griffiths CE, Foley P, Romiti R, Bachinsky M, Rottinghaus ST, Tan H, Proulx J, Valdez H, Gupta P, Mallbris L, Wolk R. Tofacitinib withdrawal and re-treatment in moderate-to-severe chronic plaque psoriasis: a randomised controlled trial. Br J Dermatol 2014 Nov 21.
20. The Latest in Dermatology Research Symposıa, 72. Annual Meeting in 2014. https://www.aad.org/File%20Library/Unassigned/AM14-Latest-in-Derm-Abstract-Book-FINAL-Version-2.pdf
21. Ports WC, Khan S, Lan S, Lamba M, Bolduc C, Bissonnette R, Papp K. A randomized phase 2a efficacy and safety trial of the topical Janus kinase inhibitor tofacitinib in the treatment of chronic plaque psoriasis. Br J Dermatol 2013; 169: 137-145.
22. Huang JF, Yafawi R, Zhang M, McDowell M, Rittenhouse KD, Sace F, Liew SH, Cooper SR, Pickering EH. Immunomodulatory effect of the topical ophthalmic Janus kinase inhibitor tofacitinib (CP-690,550) in patients with dry eye disease. Ophthalmology 2012; 119: e43-50.
23. Liew SH, Nichols KK, Klamerus KJ, Li JZ, Zhang M, Foulks GN. Tofacitinib (CP-690,550), a Janus kinase inhibitor for dry eye disease: results from a phase 1/2 trial. Ophthalmology 2012; 119: 1328-1335.
24. Wojciechowski D, Vincenti F. Targeting JAK3 in kidney transplantation: current status and future options. Curr Opin Organ Transplant 2011; 16: 614-619.
25. Zand MS. Tofacitinab in renal transplantation. Transplant Rev (Orlando) 2013; 27: 85-89.
26. Vincenti F, Silva HT, Busque S, O'Connell PJ, Russ G, Budde K, Yoshida A, Tortorici MA, Lamba M, Lawendy N, Wang W, Chan G. Evaluation of the Effect of Tofacitinib Exposure on Outcomes in Kidney Transplant Patients. Am J Transplant 2015;3.
27. van Gurp E, Weimar W, Gaston R, Brennan D, Mendez R, Pirsch J, Swan S, Pescovitz MD, Ni G, Wang C, Krishnaswami S, Chow V, Chan G. Phase 1 dose-escalation study of CP-690 550 in stable renal allograft recipients: preliminary findings of safety, tolerability, effects on lymphocyte subsets and pharmacokinetics. Am J Transplant 2008; 8: 1711-1718.
28. Borie DC, Changelian PS, Larson MJ, Si MS, Paniagua R, Higgins JP, Holm B, Campbell A, Lau M, Zhang S, Flores MG, Rousvoal G, Hawkins J, Ball DA, Kudlacz EM, Brissette WH, Elliott EA, Reitz BA, Morris RE. Immunosuppression by the JAK3 inhibitor CP-690,550 delays rejection and significantly prolongs kidney allograft survival in nonhuman primates. Transplantation 2005; 79: 791-801.
29. Boland BS, Sandborn WJ, Chang JT. Update on Janus kinase antagonists in inflammatory bowel disease. Gastroenterol Clin North Am 2014; 43: 603-617.
30. Krishnareddy S, Swaminath A. When combination therapy isn't working: emerging therapies for the management of inflammatory bowel disease. World J Gastroenterol 2014; 20: 1139-1146.
31. Coskun M, Salem M, Pedersen J, Nielsen OH. Involvement of JAK/STAT signaling in the pathogenesis of inflammatory bowel disease. Pharmacol Res 2013; 76: 1-8.
32. Vuitton L, Koch S, Peyrin-Biroulet L. Janus kinase inhibition with tofacitinib: changing the face of inflammatory bowel disease treatment. Curr Drug Targets 2013; 14: 1385-1391.

33. Fujii Y, Sengoku T. Effects of the Janus kinase inhibitor CP-690550 (tofacitinib) in a rat model of oxazolone-induced chronic dermatitis. Pharmacology 2013; 91: 207-213.

34. Yiu ZZ, Warren RB. Efficacy and safety of emerging immunotherapies in psoriasis. Immunotherapy 2015; 7: 119-133.

35. Scott LJ. Tofacitinib: a review of its use in adult patients with rheumatoid arthritis. Drugs. 2013; 73: 857-874.

36. Maiga M, Lun S, Guo H, Winglee K, Ammerman NC, Bishai WR. Risk of tuberculosis reactivation with tofacitinib (CP-690550). J Infect Dis 2012; 205: 1705-1708.

37. Krishnaswami S, Kudlacz E, Wang R, Chan G. A supratherapeutic dose of the Janus kinase inhibitor tasocitinib (CP-690,550) does not prolong QTc interval in healthy participants. J Clin Pharmacol 2011; 51: 1256-1263.

38. Lawendy N, Krishnaswami S, Wang R, Gruben D, Cannon C, Swan S, Chan G. Effect of CP-690,550, an orally active janus kinase inhibitor, on renal function in healthy adult volunteers. J Clin Pharmacol 2009; 49: 423-429.

39. Cada DJ, Demaris K, Levien TL, Baker DE. Tofacitinib. Hosp Pharm 2013; 48: 413-424.

40. Kaur K, Kalra S, Kaushal S. Systematic review of tofacitinib: a new drug for the management of rheumatoid arthritis. Clin Ther 2014; 36: 1074-1086.